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COMMUNICATION

E- and *Z*-Stereoselectivity in the preparation of enamides from glycidyl sulfonamides and carbamates†

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Treatment of glycidyl sulfonamides with LDA delivers the corresponding enesulfonamide with good selectivity for the *E*-isomer, whereas the corresponding carbamates exhibit selectivity for the *Z*-enecarbamate. An E1cB elimination mechanism proceeding from a substrate–base chelate complex is advanced as rationalisation of the latter set of *Z*-selective outcomes.

Enamides are valuable synthetic intermediates,[1] and their stereoselective preparation has attracted much recent attention from the synthetic community. In this regard, new methods for access to this functional unit have been introduced lately based on, *inter alia*, cross coupling processes;[2] hydroamination of alkynes;[3] and the Peterson reaction.[4] In relation to this and based on our on-going drug discovery programmes, we wished to prepare a range of enamines of general structure **2**, possessing different pendant nitrogen groups. We envisaged that a base-induced epoxide–allylic alcohol rearrangement[5] of the appropriately *N*-functionalised glycidyl amine **1** would represent an extremely concise entry into this series of compounds from simple starting materials (Scheme 1). Excepting a single example,[6] there have been no reports on this particular reaction variant with acyclic substrates.[7,8] Herein, we report our studies leading to substrate dependent stereoselective access to the desired *E*- and *Z*-product isomers.

Treatment of glycidylamine derivatives **1a–f** with excess LDA at −78 °C in 2-methyltetrahydrofuran (2-MeTHF), followed by warming to −60 °C over 2 h and an aqueous extractive workup, gave the results summarised in Table 1. Other than for the sterically
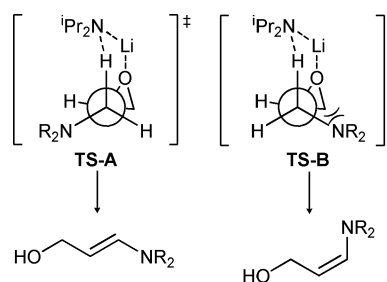
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Scheme 1

Table 1 Comparison of substrates[a]

Entry	Substrate	R[1]	R[2]	Conversion	*E* : *Z*
1	**1a**	Ts	Me	100	90 : 10
2	**1b**	Ts	Ph	100	90 : 10
3	**1c**	Boc	Me	100	50 : 50
4	**1d**	Boc	Ph	100	25 : 75
5	**1e**	Boc	^{t}Bu	20	15 : 85
6	**1f**	Boc	*p*-MeOC$_6$H$_4$	100	25 : 75

[a] Conditions: LDA (2.4 eq), 2-MeTHF, −78 °C to −60 °C, 2 h; NH$_4$Cl (aq).

hindered substrate **1e**, conversion to **2** was quantitative. However, when we came to examine the selectivity for the resultant olefin geometry, we made some notable observations, which led us to consider this reaction in more detail. Glycidyl sulfonamides **1a** and **1b** gave an identical *E* : *Z* ratio favouring the *E*-isomer. This is consistent with the *syn*-elimination mechanism advanced by Thummel and Rickborn,[9] illustrated in Fig. 1, where the lithium counterion chelates the epoxide oxygen and the amide anion. Transition state **TS-A**, leading to the *E*-product, is favoured due to the lack of an eclipsing interaction (*cf.* **TS-B**) between the epoxide methylene and the sulfonamide unit.

Fig. 1 Transition states for *syn*-elimination of **1a** and **1b**.

In contrast, glycidyl carbamates gave much higher proportions of the *Z*-isomer under the same conditions. Comparison of

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Table 2 Survey of conditions for reaction of **1f**

Entry	Solvent	Base	Equivalents	Conversion	$E:Z$
1	2-MeTHF	LDA	2.4	100	25 : 75
2	2-MeTHF	LDA[a]	2.4	100	80 : 20
3	THF	LDA	2.4	100	25 : 75
4	Toluene	LDA	2.4	100	60 : 40
5	Et$_2$O	LDA	2.4	100	60 : 40
6	2-MeTHF	LDA	1.0	50	25 : 75
7	2-MeTHF	LDA	1.5	75	25 : 75
8	2-MeTHF	LDA	2.0	100	25 : 75
9	2-MeTHF	Mg(N^{i}Pr$_2$)$_2$	2.4	100	20 : 80
10	2-MeTHF	LiTMP	2.4	100	25 : 75
11	2-MeTHF	LiNEt$_2$	2.4	100	60 : 40
12	2-MeTHF	LiNc-C$_4$H$_8$	2.4	100	75 : 25
13	2-MeTHF	LiN(^{t}amyl)$_2$	2.4	100	25 : 75

^{a} DMPU (10 molar equivalents) added.

1c–e (entries 3–5) illustrates that formation of the *Z*-isomer is proportional to the steric bulk of the carbamate *N*-substituent. That the effect is steric, and not electronic, in origin was confirmed by comparing phenyl case **1d** with that of the *p*-methoxy analogue **1f**; exactly the same *E* : *Z* ratio was obtained in each case (entries 4 and 6).
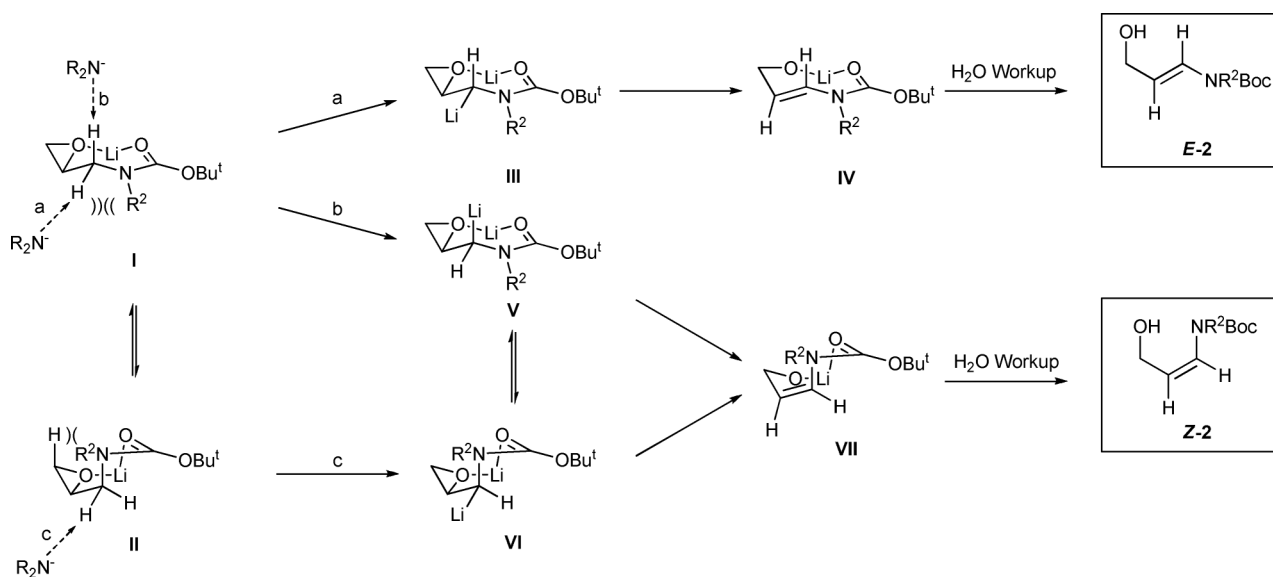
We hypothesised that in the latter glycidyl carbamate cases some additional chelation was responsible for the unusual stereoselectivity, and chose **1f** as a vehicle for further investigation. As can be seen in Table 2, addition of 10 equivalents of DMPU (entry 2) reversed the *E* : *Z* selectivity to 80 : 20. As the presence of excess DMPU would be expected to disrupt any metal–substrate chelation, an alternative *anti*-elimination[10] may be propounded, where the carbamate subtends the methylene group in **TS-D**, leading to a higher energy transition state for formation of the *Z*-isomer, Fig. 2.

We next investigated reagent stoichiometry, and found that a twofold excess of base was required for full conversion (Table 2, entries 6–8). Alternative solvents (entries 3–5) and bases (9–13)[11] were also surveyed. Whilst the solvent pattern is less

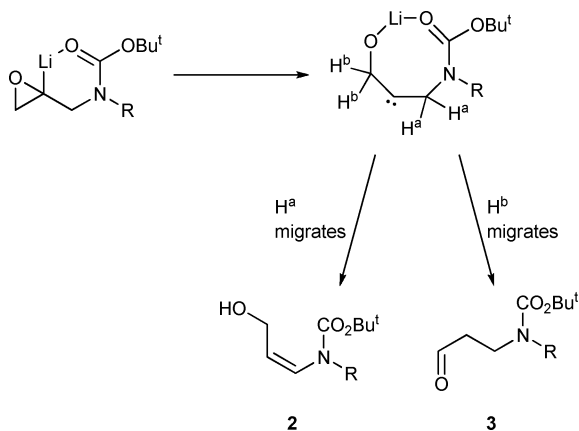**Fig. 2** *anti*-Elimination in the presence of excess DMPU.

explicable, a clear trend is apparent in the base comparison, with increasing base size giving enhanced *Z*-selectivity. Taken with the results in Table 1, it suggests that formation of the *E*-product is increasingly disfavoured by a steric interaction between R groups on the substrate and those connected to the base reagent nitrogens. Furthermore, the selectivity appears to be kinetic, not thermodynamic in origin: subjection of pure **E-2c**[12] to the reaction conditions did not result in the formation of observable levels of **Z-2c**.

The results, showing the selective formation of the *Z*-enecarbamate, are consistent with the formation of a chelated complex between substrate and base (**I** or **II**, Scheme 2), followed by attack of a second equivalent of base upon this intermediate, to deliver a product that does not then dissociate the complexed base prior to workup. Conformation **I** would be favoured over **II** due to the less desirable flagpole-like steric interactions in the latter. Attack of base to remove a proton from **I** could proceed along trajectory *a* or *b*, removing the *pseudo*-equatorial proton (leading to the *E*-product), or the *pseudo*-axial proton (leading to the *Z*-alkene), respectively. Orbital overlap between the breaking C–O bond and the abstracted proton on path *a* is superior to that of path *b*, so this would normally be favoured on stereoelectronic grounds. This would give rise to the *E*-product *via* an E1cB (bordering on E2) mechanism, proceeding through intermediate **III**. However, returning to intermediate **I**, the R group on the

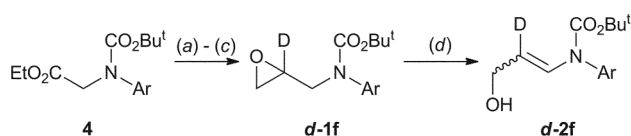**Scheme 2** Proposed course of elimination *via* substrate–base complex.

adjacent nitrogen is closer to the proton which would be abstracted *via* path *a*. Accordingly, as this group, or the base, is increased in size, attack along this trajectory becomes disfavoured. On the other hand, abstraction of the *pseudo*-axial proton (path *b*) would give a carbon–lithium bond with poor orbital overlap towards the breaking C–O bond (structure **V**). Rotation to align the bonds for maximum orbital overlap would place the nitrogen substituent in a *syn* relationship with the epoxide methylene group, and ultimately deliver the *Z*-olefin by an unambiguously E1cB pathway. It is also worth noting that the *Z*-product would also be obtained if deprotonation took place on chelate **II** *via* trajectory *c*, driven by both steric factors and optimal orbital overlap with the breaking C–O bond.

An alternative pathway by which formation of **Z-2** would be favoured involves directed α-metallation of the epoxide[13] leading to formation of a carbenoid species, followed by H-migration (Scheme 3). It is not obvious why the latter process should be selective to formation of **2** (H^a migration) over the alternative aldehyde product **3** (H^b migration). Nevertheless we took steps to exclude this possibility. We prepared deutero-labelled *d*-**1f** by the sequence illustrated in Scheme 4, subjected this species to LDA under the now standard reaction conditions, and observed complete incorporation of deuterium in both isomers of the product *d*-**2f**, thus ruling out any mechanism involving α-metallation.

Scheme 3 Alternative carbenoid mechanism.

In conclusion, upon treatment with amide bases, glycidyl carbamates undergo elimination to give enecarbamates with selectivity for the *Z*-isomer, in contrast to the *E*-selectivity observed for the corresponding glycidyl sulfonamides. Based on a series

Conditions: (*a*) LiBD$_4$, THF, 20 °C; (*b*) (COCl)$_2$, DMSO, iPr$_2$NEt, CH$_2$Cl$_2$; (*c*) Me$_3$SOI, NaH, DMSO, 60 °C; (*d*) LDA (2.4 eq), 2-MeTHF, -78 °C to -60 °C, 4 h; NH$_4$Cl (aq)

Scheme 4 Preparation of deuterated analogue.

of observations with a range of substrates and a selection of bases, both possessing varying degrees of steric bulk, an E1cB mechanism, proceeding from a chelated intermediate, has been proposed to account for this phenomenon. We anticipate that these accumulated outcomes will be valuable to others within the preparative community, and especially in the planning of access to enamides of specific double bond geometry. Further mechanistic studies relating to this interesting reaction will be reported in due course.

Acknowledgements

Notes and references

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